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acids in the acceptor immunoglobulin heavy chain framework, at positions in the immunoglobulins wherein:

(I) the amino acid is immediately adjacent to one of the CDRs, or
(II) the amino acid is capable of interacting with the CDRs, or
(III) the donor amino acid is typical at its position for human immunoglobulin sequences, and the replaced amino acid is rare at its position for human immunoglobulin sequences.

109. (New) A humanized immunoglobulin according to claim 108, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1} .

BJ 110. (New) A humanized immunoglobulin having a complementarity determining region from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen, wherein said humanized immunoglobulin comprises at least three amino acids from the donor immunoglobulin heavy chain framework outside the Kabat CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain framework, at positions in the immunoglobulins where:

(I) the amino acid is immediately adjacent to one of the CDRs, or
(II) the amino acid is capable of interacting with the CDRs.

111. (New) A humanized immunoglobulin according to claim 110, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1} .

112. (New) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain

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variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises at least three amino acids from the donor immunoglobulin heavy chain framework outside the Kabat CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain framework, and each of these said donor amino acids:

is capable of interacting with the CDRs.

113. (New) A humanized immunoglobulin according to any one of claims 108 through 112, wherein said humanized immunoglobulin is an antibody tetramer, Fab, or (Fab')₂.

114. (New) A humanized immunoglobulin according to any one of claims 108 through 112, which is substantially pure.

115. (New) A pharmaceutical composition comprising a humanized immunoglobulin according to claim 114 in a pharmaceutically acceptable carrier.

116. (New) A humanized immunoglobulin comprising a complementarity determining region from a donor immunoglobulin and an acceptor immunoglobulin variable region framework, which humanized immunoglobulin specifically binds to an antigen, wherein the acceptor immunoglobulin variable region framework is a consensus framework from many human antibodies.

117. (New) A humanized immunoglobulin according to claim 116, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1} .

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118. (New) A humanized immunoglobulin according to claim 116, wherein said humanized immunoglobulin binds to the antigen with an affinity constant within about four-fold that of the donor immunoglobulin.

119. (New) A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, wherein the acceptor immunoglobulin heavy chain variable region framework is a consensus of human immunoglobulin heavy chain variable region frameworks, and wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside the CDRs that replace the corresponding amino acids in the acceptor immunoglobulin framework, at positions in the immunoglobulins where the amino acid is capable of interacting with the CDRs.

120. (New) A humanized immunoglobulin according to claim 119, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1} .

121. (New) A humanized immunoglobulin according to claim 119, wherein said humanized immunoglobulin binds to the antigen with an affinity constant within about four-fold that of the donor immunoglobulin.

122. (New) A humanized immunoglobulin according to any one of claims 116 through 121, wherein said humanized immunoglobulin is an antibody tetramer, Fab, or (Fab)₂.

123. (New) A humanized immunoglobulin according to any one of claims 116 through 121, which is substantially pure.

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124. (New) A pharmaceutical composition comprising a humanized immunoglobulin according to claim 123 in a pharmaceutically acceptable carrier.

125. (New) A method of producing a humanized immunoglobulin that specifically binds to an antigen, comprising the steps of:

(1) selecting an acceptor heavy chain variable region framework whose sequence is a consensus sequence of human heavy chain variable region framework sequences;

(2) synthesizing a DNA segment encoding a humanized heavy chain variable region, comprising complementarity determining regions (CDRs) from a donor immunoglobulin heavy chain variable region and the selected acceptor heavy chain variable region framework;

(3) introducing a DNA segment encoding the humanized immunoglobulin heavy chain variable region and a DNA segment encoding a humanized immunoglobulin light chain variable region into a cell; and

(4) expressing the DNA segments in the cell to produce the humanized immunoglobulin.

126. (New) The method of claim 125, further comprising the step of substituting an amino acid in the acceptor heavy chain variable region framework outside the CDRs with the corresponding amino acid from the donor heavy chain variable region, wherein the amino acid is capable of interacting with the CDRs.

127. (New) The method of claim 125, further comprising the step of purifying the humanized immunoglobulin.

128. (New) The method of claims 125 or 126, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1} .

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129. (New) A method of producing a humanized immunoglobulin that specifically binds to an antigen, the method comprising:

providing a cell containing DNA segments encoding humanized light and heavy chain variable regions; and expressing the DNA segments in the cell to produce the humanized immunoglobulin;

wherein the cell containing the DNA segments was produced by:

(1) selecting an acceptor heavy chain variable region framework whose sequence is a consensus sequence of human heavy chain variable region framework sequences;

(2) synthesizing a DNA segment encoding a humanized heavy chain variable region, comprising a complementarity determining region (CDR) from a donor immunoglobulin heavy chain variable region and the selected acceptor heavy chain variable region framework and further comprising amino acids from the donor immunoglobulin heavy chain framework outside the CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain framework, at positions in the immunoglobulins where the amino acids are capable of interacting with the CDRs;

(3) introducing a DNA segment encoding the humanized immunoglobulin heavy chain variable region and a DNA segment encoding a humanized immunoglobulin light chain variable region into a cell.

130. (New) The method of claim 129, further comprising the step of purifying the humanized immunoglobulin.

131. (New) The method of claims 129 or 130, wherein said humanized immunoglobulin binds to the antigen with an affinity constant of at least 10^8 M^{-1} .

132. (New) The method of claims 129 or 130, wherein said humanized immunoglobulin is an antibody tetramer, Fab, or (Fab')₂.